Original Article

Surgical Treatment and Follow-up Results of Pituitary ACTH Microadenoma: 18 Years' Experience

Weiguo Zhao, Shikuen Zhan, Yu Cai, Jiankang Shen and Tianxi Zhang, Department of Neurosurgery, Rui Jin Hospital of Shanghai Second Medical University, Shanghai, People's Republic of China.

OBJECTIVE: To review retrospectively our clinical experience with surgical treatment and follow-up of pituitary adrenocorticotropic hormone (ACTH) microadenomas at Rui Jin Hospital of Shanghai Second Medical University.

METHODS: Eighty-seven patients with ACTH microadenomas underwent surgery via the transsphenoidal approach. Preoperative computed tomography and/or magnetic resonance imaging revealed microadenomas in only 46 patients and was negative in the remaining 41 patients, which were classified as microadenoma grade 0. High-dose dexamethasone (Dx) suppression testing was positive in 86% of patients and low-dose Dx suppression testing was negative in all patients.

RESULTS: Histological confirmation of ACTH microadenoma was made in all 87 cases, with a minimum tumour size of only 1 to 2 mm in diameter. The remission rate was 82% for grade I and 92% for grade 0 microadenomas during 2 to 18 years of follow-up.

CONCLUSIONS: Neuroimaging studies have limited value in diagnosing ACTH grade 0 microadenoma. Clinical manifestation combined with positive Dx suppression testing is decisive in these circumstances. Surgical intervention could achieve a high relief rate for ACTH microadenomas, especially in grade 0 group. *(Asian J Surg* 2003;26(1):22–5)

Introduction

Cushing's disease, which implies an aetiological origin in the pituitary, accounts for about 70% of all causes of Cushing's syndrome. Approximately 90% of adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas are less than 10 mm in diameter and some of them are less than 3 mm.[1,2] This characteristically small tumour size often makes a neuroimaging diagnosis ambiguous, even with the most advanced helical computed tomography (CT) or magnetic resonance imaging (MRI). Thus, the surgical indications are sometimes controversial. We retrospectively analyzed our surgical experience, including 18 years of follow-up, for 87 cases of pituitary ACTH microadenoma.

Patients and methods

From September 1984 to September 2000, 87 patients with pituitary ACTH microadenomas underwent surgery via the transsphenoidal approach, which accounted for 78% of all surgically treated ACTH adenoma cases in the same period. There were 67 women and 20 men, ranging in age from 16 to 53 years, with a mean of 33 years. The average duration of illness before operation was 2.6 years. Clinically, all patients had typical signs of Cushing's syndrome. On biochemical studies, absent diurnal cortisol rhythm with abnormally high free cortisol levels in urine were found in all patients. All patients had a high level of plasma cortisol, except for four, whose cortisol level was just within the upper normal limit. On dexamethasone (Dx) suppression testing,

Address reprint requests to Professor Weiguo Zhao, Department of Neurosurgery, Rui Jin Hospital of Shanghai Second Medical University, Shanghai 200025, People's Republic of China.
E-mail: rjneurosurgery@yahoo.com.cn • Date of acceptance: 2nd October, 2002

the urine cortisol level could be suppressed by a high dose of Dx (8 mg) in 86% of patients, but not by a low dose of 2 mg in all cases. We believe this is a reliable and sensitive index for screening of ACTH adenoma from Cushing's syndrome of other causes, such as Cushing's syndrome of adrenal origin. Peripheral ACTH concentrations were all within the normal limits, except for three that were slightly higher than reference value (12–78 pg/mL), with an average of 37 ± 23 pg/mL.

On neuroimaging studies, microadenomas were identified by enhanced CT alone in 21 cases and by both CT and MRI in 25 cases. These cases were classified as grade I microadenomas. The remaining 41 cases appeared normal on CT and MRI, with normal contours of the sella turcica on 1-mm, thin-section pluridirectional CT. These cases were grouped as grade 0 microadenomas. The average height of the pituitary gland ranged from 6 mm for grade 0 to 9 mm for grade I. Deviation of the pituitary stalk was found in 67% of grade I microadenomas.

All operations were made through a sublabial or endonasal, unilateral-septal transsphenoidal approach. Generally, after opening the dura, yellowish semiliquid tumour tissue bulged from the sellar. This was not the situation with most grade 0 microadenomas. Usually normal-appearing pinkish pituitary tissue was first encountered after opening the dura of the sellar floor. Careful exploration of the pituitary was then made by horizontal and vertical incisions of the gland until a tumour was found and confirmed by intraoperative frozen section histology. In rare cases, when the texture and colour of the adenoma tissue was suspicious and intraoperative cytology did not reveal a definitive diagnosis of adenoma, hemihypophysectomy was performed to ensure a successful outcome.

Results

Surgical and pathological findings

Selective adenomectomy was achieved in 81 of 87 patients. Six patients underwent hemihypophysectomy on the tumour side either because the tumour was too tiny or its nature was diffusely invasive, or because of an ambiguous intraoperative diagnosis. Most of the adenomas were single in origin, but we found multifocal tumours embedded in the pituitary glands of four patients. Central wedge tumours were found in 39 patients, while the remaining tumours were found in the lateral wings of the pituitary glands. The sizes of adenomas extirpated are shown in the Table. Intraoperative frozen section revealed an adenoma diagnosis in 78 patients, and postoperative histopathological confirmation of microadenoma was made in all 87 patients, with minimal tumour sizes as small as 1 to 2 mm in diameter. Immunohistochemical analyses were done in 49 cases, which showed ACTH-positive staining in 52% and polyhormonal-positive staining in 48% of all cases.

Complications and outcomes

All patients recovered well. There was no mortality or major complication among the treated patients. Postoperative hypopituitarism occurred in 11 patients, of which it was temporary in eight; the remaining three patients required permanent cortisone replacement therapy. Postoperative transient diabetes insipidus occurred in four patients, and temporary cerebrospinal fluid rhinorrhoea occurred in another five patients. There were nine patients with postoperative syndrome of inappropriate secretion of antidiuretic hormone (SIADH). All recovered well with proper management. Three patients had complications of adrenoadenoma and underwent adrenoadenomectomy 4 months after their initial pituitary surgery.

Clinical and endocrinological remission was observed in 79 patients, including six patients in whom cortisol levels normalized 2 to 4 months after surgery. Eight patients did not benefit from pituitary surgery. This surgical failure might be attributed to possible partial adenomectomy or multifocal microadenomas in the pituitary, which were probably missed during surgery.

Follow-up

Clinical and/or biochemical follow-up was performed on an outpatient basis or by questionnaire in 69 out of 79 surgically effective cases. Remission was defined as normalization of

Table. Size of adrenocorticotropic hormone microadenomas surgically extirpated*

Diameter	Microadenoma grade		Total
	0	I	
< 2 mm	10	1	11
3–5 mm	32	13	45
6–9 mm		34	34
Total	42	48	90

*Includes multifocal microadenomas.

serum cortisol level and relief of Cushing's symptoms. The remission rate was 82% (27/33) for grade I and 92% (33/36) for grade 0 microadenomas during the 2- to 18-year follow-up period (mean, 7.5 yr). Nine patients had recurrences after an apparent remission of as long as 5 years. They received radiotherapy as an alternative treatment.

Discussion

Transsphenoidal microsurgery for the treatment of Cushing's disease is a standard procedure nowadays. With the development of advanced imaging study techniques, more pituitary microadenomas are clearly shown on thin-slice, dynamic, enhanced CT or MRI. This makes the decision to operate both reasonable and acceptable to patients, and good results can be expected.[3] To manage a case of pituitary adenoma without imaging confirmation is difficult and remains a challenge to neurosurgeons, who bear the responsibility if a negative exploration is encountered.

Simultaneous venous sampling from both the inferior petrosal sinuses (IPS) and a peripheral (P) vein for measurement of ACTH production, with corticotropin-releasing hormone stimulation, can be useful in diagnosing and localizing the existence of intra-pituitary ACTH-secreting adenomas.[4,5] The test is considered positive for lateralization when the side-to-side ACTH ratio is greater than 1.4 or when the peak IPS/P ACTH ratio is greater than 3. Semple et al reported 91% accuracy in predicting tumour location (side) as compared to surgical findings,[2] whereas others claimed to have only 50% correlation with surgical findings.[5] IPS sampling is not routinely performed in many clinical practices due to its inconvenient manipulation. Furthermore, it cannot replace neurosurgical experience, which remains the most important predictive factor for outcome in surgical management of Cushing's disease.

In Cushing's disease, most ACTH-secreting adenomas are microadenomas. As seen in our series of patients, nearly half of the microadenomas could not be identified on MRI and/or CT. The minimum size of a microadenoma detectable by MRI is reported to be 3 mm. Nonetheless, the existence of tiny adenomas less than 3 mm in diameter is not rare in cases of Cushing's disease. Should we rely on imaging diagnosis for Cushing's disease and delay surgery until the tumour is visible on imaging studies? The answer is definitely "No." Unlike the case of prolactinoma, even when clinical and biological evidence suggests the diagnosis, operation is reserved until confirmed by neuroimaging studies because there is an extremely effective drug (bromocriptine) that can well control the disease. Because there is no effective conservative remedy for Cushing's disease, aggressive surgical intervention is the treatment of choice.

According to our experience, as long as the clinical and biochemical diagnosis is correct, and a positive high-dose Dx suppression test revealed disease of pituitary origin rather than adrenal origin, surgical intervention is always indicated. During the operation, correct visual interpretation of the yellowish adenomatous tissue removed by an experienced neurosurgeon is extremely important. The tumour tissue not only differs from the surrounding pinkish normal pituitary tissue, but also has a difference in texture, which is usually crisp and easy to remove.

In some of our patients, Cushing's disease was complicated by adrenal adenomatous proliferation or nodular adrenoadenoma. It is our policy to treat the pituitary adenoma first and then monitor the patient closely for at least 3 to 4 months. Toms et al observed postoperative changes of cortisol levels and found that there was still autonomous secretion of cortisol by proliferated adrenal cortex for 2 weeks after pituitary ACTH adenomectomy, and the lowest serum cortisol level was reached 6 to 12 weeks after the operation.[6] Thus, only when hypercortisolaemia has not resolved after that period is adrenoadenomectomy indicated.

Conclusions

Imaging studies have limited value in diagnosing grade 0 ACTH microadenoma. Clinical manifestation combined with a positive Dx suppression test is decisive in these circumstances. Even though radiographically occult, these minute adenoma can be identified intraoperatively, selectively extirpated, verified histologically and as a result, long-term remission can be achieved for those otherwise medically intractable patients.

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